

## Elizabethkingia anophelis: Clinical Experience of an Academic Health System in Southeastern Wisconsin

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In late 2015 and early 2016, 11 patients were identified with cultures positive for *Elizabethkingia anophelis* in our health system. All patients had positive blood cultures upon admission. Chart review showed that all had major comorbidities and recent health care exposure. The attributable mortality rate was 18.2%.

**Keywords.** *Elizabethkingia*; outbreak; Wisconsin.

*Elizabethkingia*, a Gram-negative, obligate aerobic bacillus, was classified until 2005 under the families *Flavobacteriaceae* and *Chryseobacterium* [1]. *Elizabethkingia* is considered an emerging pathogen in the health care environment [2] and is implicated in cases of neonatal meningitis and sepsis [3] and nosocomial pneumonia [4]. *E. anophelis*, a novel species within the genus, was first identified in 2011 [5] and has been implicated in similar infections [6]. Starting in late 2015, an increased number of *Elizabethkingia* infections were identified in Southeastern Wisconsin. From November 2015 to May 2016, 63 cases of *E. anophelis* were reported to the Wisconsin Division of Public Health. Cases eventually spanned 3 states (Wisconsin, Illinois, Michigan) and made up the largest outbreak of *E. anophelis* ever described. Despite an exhaustive outbreak investigation by state and federal authorities, the source of the outbreak has not been determined [7, 8]. We now aim to describe the clinical

experience with *E. anophelis* at our health care system during the 2015–2016 outbreak.

### METHODS

This was a retrospective case series of all consecutive patients admitted to Froedtert Health System hospitals with positive cultures for *Elizabethkingia*, *Flavobacterium*, and *Chryseobacterium* from November 2015 to June 2016. Froedtert Health is located in Southeastern Wisconsin and is comprised of Froedtert Memorial Lutheran Hospital in Milwaukee (total staffed beds, 518; total patient-days per year, 140 279), Community Memorial Hospital in Menomonee Falls (total staffed beds, 202; total patient-days per year, 30 227) and St. Joseph's Hospital in West Bend (total staffed beds, 70; total patient-days per year, 15 765). The microbiology records were retrospectively searched for cultures positive for *Elizabethkingia* spp., *Flavobacterium* spp., and *Chryseobacterium* spp. [1] from specimens obtained from any body site, with specimen collection dates since January 1, 2011, as requested by the Bureau of Communicable Diseases, Wisconsin Division of Public Health. Medical records of identified cases were summarized after chart review. Patient information collected for the study included demographic data (age, sex, county of residence), past medical history, clinical presentation, culture source, antibiotic therapy, previous contact with hospitals within our health care system 30 days prior to detection of *Elizabethkingia*, and mortality data. Blood cultures not identified by the Verigene system (Luminex Madison, WI) underwent cultivation on routine media, with preliminary identification and susceptibility testing utilizing matrix-assisted laser desorption/ionization time-of-flight (MALDI-ToF MS, Bruker Daltonics Inc., Billerica, MA) and susceptibilities performed by BD Phoenix (BD, Franklin Lakes, NJ) at Froedtert Memorial Lutheran Hospital and Community Memorial Hospital, as well as a conventional overnight microscan (Beckman Coulter, Inc, Indianapolis, IN) panel at St. Joseph's Hospital. Isolates were sent to the Wisconsin State Laboratory of Hygiene for additional characterization. Descriptive statistics were performed in R Studio 1.0.44 (RStudio, Inc., Boston, MA), utilizing the R statistical language, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). A waiver for informed consent was granted by the Medical College of Wisconsin Institutional Review Board.

### RESULTS

During the 8 months of surveillance, a total of 13 patients were identified. Eleven (84.6%) were identified upon admission to our system (Table 1), and 2 (15.4%) were positive at transferring facilities prior to admission to our system. From the 11 cases identified in our system, 6 cases were initially identified as *F. meningosepticum*, and 4 were identified as *E. meningosepticum*.

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**Table 1. Line List of Patients With *Elizabethkingia anophelis* Infection**

Patient	Age	Sex	Admission Date, mo/y	Hospital	Past Medical History and Initial Presentation	Days From Admission to Positive Culture	Source of Culture	Susceptibility	Antibiotic Therapy, d	Died
1	84	M	Nov/2015	CMH	DM type 1, ESRD on dialysis. Presented with sepsis, altered mental status, suspected pneumonia.	1	B	CIP, LEV, TMP/SMX	CIP (14)	No
2	80	F	Dec/2015	SJH	DM, CKD stage 3, COPD, lung cancer. Presented with dehydration, sepsis, and suspected UTI, with isolation of <i>Aerococcus urinae</i> in urine.	1	B	CIP, LEV, TMP/SMX	CIP (15)	No
3	55	M	Dec/2015	FH	DM, drug/alcohol abuse, chronic HCV infection, hepatocellular carcinoma. Presented with right shoulder pain, fever, and fatigue, requiring irrigation and debridement of joint.	1	B, Syn	CEF, CIP, PIP/TAZ, TMP/SMX; CIP, PIP/TAZ, TMP/SMX (synovial fluid)	CIP (28)	No
4	64	F	Jan/2016	SJH	DM, ESRD on dialysis. Presented with altered mental status. Urine culture with <i>Klebsiella pneumoniae</i> resistant to ampicillin.	1	B	CIP, LEV, TMP/SMX	VAN/CIP (14)	No
5	58	M	Jan/2016	SJH	DM, alcohol abuse, pancreatitis, depression. Found unresponsive at home, with PEA and hyperglycemia. Died within 24 hours of initial assessment.	1	B	CIP, TMP/SMX	-	Yes
6	69	M	Feb/2016	SJH	COPD, metastatic lung cancer. Presented with right lower extremity erythema and warmth and fever, suggestive of cellulitis.	1	B	CIP, LEV, TMP/SMX, PIP/TAZ	CIP (14)	No
7	81	F	Feb/2016	SJH	CKD, COPD, recurrent right-sided pleural effusion requiring thoracentesis. Presented with acute respiratory failure, sepsis. Initially managed with noninvasive positive pressure ventilation and thoracentesis, then requiring endotracheal intubation. After return of respiratory distress following extubation, comfort care was instituted.	1	B, S, P, Br	CIP, LEV, TMP/SMX	CIP/TMP/SMX (3) plus PIP/TAZ (4)	Yes
8	82	F	Feb/2016	FH	CKD, COPD, neurogenic bladder with ureteral obstruction and bilateral nephrostomy tubes. Presented with altered mental status, fever, dyspnea, and abnormal urinalysis, with urine culture positive for <i>Pseudomonas aeruginosa</i> . Nephrostomy tube exchange.	1	B	CIP, TMP/SMX	VAN/CIP (42)	No
9	84	F	Mar/2016	FH	Chronic HCV infection, cirrhosis, DM type 2, alcohol abuse. Presented with abdominal distention, fever, headache, and myalgias. Suspected spontaneous bacterial peritonitis. Patient died 4.5 months after <i>E. anophelis</i> isolation ( <i>E. coli</i> /bacteremia and spontaneous bacterial peritonitis).	2	B, S, A	CIP, PIP/TAZ, TMP/SMX; CEF, CIP, PIP/TAZ, TMP/SMX (sputum)	CIP/PIP/TAZ (14)	No
10	73	M	Apr/2016	SJH	DM, pancreatic cancer. Presented with altered mental status, hypoglycemia, and left lower extremity erythema and warmth, suspicious for cellulitis.	1	B	CIP, LEV, TMP/SMX	CIP/TMP/SMX (14)	No
11	49	F	Jun/2016	FH	ESRD on dialysis, failed renal transplant, splenectomy after immune thrombocytopenic purpura, Hodgkin lymphoma. Presented with dehydration, persistent <i>Elizabethkingia</i> bacteremia, transesophageal echocardiogram with right atrium mass attached to central access. Line change and prolonged antibiotic therapy, adjusted after concerns with thrombocytopenia related to sulfa.	7	B	MIN, PIP/TAZ, TMP/SMX	MIN/RIF (42)	No

Abbreviations: A, ascitic fluid; B, blood; Br, bronchial lavage; CEF, cefepime; CIP, ciprofloxacin; CKD, chronic kidney disease; COPD, chronic obstructive lung disease; CMH, Community Memorial Hospital; DM, diabetes; ESRD, end-stage renal disease; F, Female; FH, Froedtert Hospital; HCV, hepatitis C virus; LEV, levofloxacin; M, Male; MIN, minocycline; P, pleura; PEA, pulseless electrical activity; PIP/TAZ, piperacillin/tazobactam; RIF, rifampin; S, sputum; SJH, St. Joseph's Hospital; Syn, synovial fluid; TMP/SMX, trimethoprim/sulfamethoxazole; UTI, urinary tract infection; VAN, vancomycin.

Out of the 11 patients recognized at our system, 54.6% were female and the mean age was 70.8 years (range, 49–84 years). All patients had positive blood cultures on admission, with 9 (81.8%) becoming positive in the first 24 hours after admission (range, 1–7 hours). Five of the 11 cases had bacteremia lasting for more than 24 hours (range, 1–4 hours; median, 1 hour). One patient had positive blood, pleural fluid, and sputum cultures, and 1 patient had positive blood and synovial fluid cultures. Patients were admitted to our system with a myriad of presentations, including hyperglycemia, hypoglycemia, *Klebsiella pneumoniae* urinary tract infection, respiratory failure, cellulitis, and change in mental status. Most patients were transferred from home, although all had health care exposures within our health care system prior to detection of *Elizabethkingia* spp. Comorbidities included cancer (n = 5), such as lung cancer, hepatocellular carcinoma, pancreatic adenocarcinoma, and Hodgkin's lymphoma, chronic obstructive pulmonary disease (n = 4), diabetes (n = 7), end-stage renal disease on hemodialysis (n = 3), and alcoholism (n = 3). Two patients died within 30 days of a positive *E. anophelis* culture (attributable mortality rate, 18.2%). Both died during the admission when *Elizabethkingia* was identified. One patient (Table 1, patient 9) died 4.5 months after isolation of *E. anophelis* (spontaneous bacterial peritonitis with isolation of *E. coli* in ascitic fluid and blood cultures).

## CONCLUSIONS

From November 2015 to June 2016, 11 patients were identified in our health system with cultures positive for *E. anophelis*. All patients had positive blood cultures at the time of hospital admission. *E. anophelis* was identified in both sterile and nonsterile body fluids. All patients had at least 1 major comorbidity, including but not limited to cancer, chronic obstructive pulmonary disease, diabetes, end-stage renal disease requiring hemodialysis, and alcohol abuse. The mortality rate was high (18.2% of patients admitted to our hospital system), and 1 patient died 4 months after initial isolation. These findings seem to reflect the information released by state and federal authorities [7, 8].

Outbreaks by *Elizabethkingia* have been previously described in the literature [2–4, 6]. Most of these reports are attributed to *E. meningoseptica*, but misidentification of *E. anophelis* as *E. meningoseptica* could underestimate the number of cases attributed to this species. This phenomenon has been attributed to MALDI-TOF without up-to-date reference spectrum databases [9]; therefore, the increased number of cases could be related to better detection rather than emergence of a new pathogen. There have been descriptions of neonatal transmission causing neonatal meningitis, with molecular evidence suggesting vertical transmission from a mother with chorioamnionitis. The mechanism of colonization of the mother could not be identified. Environmental contamination was not found [6]. In contrast, another outbreak report described contaminated taps and aerators with this organism in an intensive care unit [3]. In this

report, *Elizabethkingia* infection was associated with systemic inflammatory response syndrome in more than half of patients with isolation of *E. meningoseptica*. Five patients died (mortality rate, 17%) during this outbreak. Acquisition was associated with contaminated water sources in the critical care unit.

Our study is limited to patients admitted to hospital facilities within a narrow geographical area experiencing an outbreak by a single strain [9]. This might not be representative of the complete scope of infections with *E. anophelis*. During the outbreak investigation, the Wisconsin Division of Public Health cultured sinks and faucets in our facilities and failed to isolate *Elizabethkingia*. This suggests that environmental contamination was not a salient feature of this outbreak. The mortality rate noted in our health care system seems to be within the range of previous reports. The isolation of *E. anophelis* in blood cultures in all cases is striking, which could suggest either dissemination from nonsterile sites or direct contamination into the bloodstream. We cannot rule out a long incubation period prior to development of symptoms based on our findings, but the initial presentation of bacteremia in all patients makes this hypothesis less likely.

Our observations suggest that *E. anophelis* is a true pathogen, especially in patients with multiple comorbidities. Isolation of *Elizabethkingia* in sterile fluid should never be considered a contaminant. Combination antibiotic therapy pending susceptibility data is recommended, given the presence of multiple mechanisms of antimicrobial resistance [2, 6, 9]. Empirical treatment should include piperacillin/tazobactam plus quinolone, rifampin, or minocycline. Vancomycin has been used in severe infections, especially in meningitis [2]. Duration of therapy has not been evaluated in clinical trials. It should be dictated by the clinical situation, with prolonged courses for deep-seated infection. Treatment can be complicated by the ability of *E. anophelis* to develop biofilms [3, 4]. Ruling out meningitis in a patient with altered mental status is crucial, given the ability of this organism to invade the central nervous system [6]. From an infection prevention standpoint, active surveillance including environmental sampling of hospital water system components, infusion containers, and parenteral and antiseptic solutions, along with enhanced terminal cleaning and the establishment of contact isolation precautions to contain dissemination, have been advocated in outbreaks involving hospital areas caring for patients with complex medical issues [2, 3, 7]. The clinical community ought to increase their awareness of *Elizabethkingia* as an emerging pathogen, and further studies should be performed to better determine its pathogenicity, modes of transmission, and optimal treatment.

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